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(54) PYRAZOLOPYRIMIDINONES FOR THE TREATMENT OF IMPOTENCE

PYRAZOLPYRIMIDINONE FÜR DIE BEHANDLUNG VON IMPOTENZ

PYRAZOLOPYRIMIDINONES UTILISEES POUR TRAITER L'IMPUISSANCE

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H419 - H422 F. TRIGO-ROCHA ET AL. 'Nitric
oxide and cGMP: mediators of pelvic nerve-
stimulated erection in dogs'**

Remarks:

The file contains technical information submitted
after the application was filed and not included in
this specification

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Description

This invention relates to the use of a series of pyrazolo[4,3-d]pyrimidin-7-ones for the preparation of a medicament for the treatment of impotence.

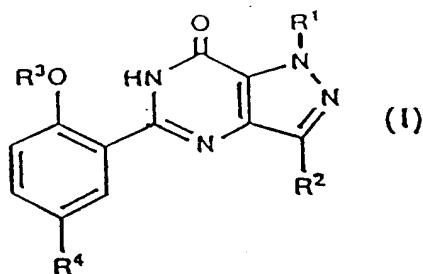
Impotence can be defined literally as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of organic rather than of psychogenic origin.

Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c. injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E₁, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been shown to be effective but produces side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004, namely in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

Unexpectedly, it has now been found that these disclosed compounds are useful in the treatment of erectile dysfunction. Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration. Thus the present invention concerns the use of a compound of formula (I):



wherein

R¹ is H; C₁-C₃ alkyl; C₁-C₃ perfluoroalkyl; or C₃-C₅ cycloalkyl;

R² is H; C₁-C₆ alkyl optionally substituted with C₃-C₆ cycloalkyl; C₁-C₃ perfluoroalkyl; or C₃-C₆ cycloalkyl;

R³ is C₁-C₆ alkyl optionally substituted with C₃-C₆ cycloalkyl; C₁-C₆ perfluoroalkyl; C₃-C₅ cycloalkyl; C₃-C₆ alkenyl; or C₃-C₆ alkynyl;

R⁴ is C₁-C₄ alkyl optionally substituted with OH, NR⁵R⁶, CN, CONR⁵R⁶ or CO₂R⁷; C₂-C₄ alkenyl optionally substituted with CN, CONR⁵R⁶ or CO₂R⁷; C₂-C₄ alkanoyl optionally substituted with NR⁵R⁶; (hydroxy)C₂-C₄ alkyl optionally substituted with NR⁵R⁶; (C₂-C₃ alkoxy)C₁-C₂ alkyl optionally substituted with OH or NR⁵R⁶; CONR⁵R⁶; CO₂R⁷; halo; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; SO₂NR⁹R¹⁰; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;

R⁵ and R⁶ are each independently H or C₁-C₄ alkyl, or together with the nitrogen atom to which they are attached

form a pyrrolidinyl, piperidino, morpholino, 4-N(R¹¹)-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;

R⁷ is H or C₁-C₄ alkyl;

R⁸ is C₁-C₃ alkyl optionally substituted with NR⁵R⁶;

R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R¹²)-piperazinyl group wherein said group is optionally substituted with C₁-C₄ alkyl, C₁-C₃ alkoxy, NR¹³R¹⁴ or CONR¹³R¹⁴;

R¹¹ is H; C₁-C₃ alkyl optionally substituted with phenyl; (hydroxy)C₂-C₃ alkyl; or C₁-C₄ alkanoyl;

R¹² is H; C₁-C₆ alkyl; (C₁-C₃ alkoxy)C₂-C₆ alkyl; (hydroxy)C₂-C₆ alkyl; (R¹³R¹⁴N)C₂-C₆ alkyl; (R¹³R¹⁴NOC)C₁-C₆ alkyl; CONR¹³R¹⁴; CSNR¹³R¹⁴; or C(NH)NR¹³R¹⁴;

and

R¹³ and R¹⁴ are each independently H; C₁-C₄ alkyl; (C₁-C₃ alkoxy)C₂-C₄ alkyl; or (hydroxy)C₂-C₄ alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms, alkenyl and alkynyl groups having four or more carbon atoms, alkoxy groups having three carbon atoms and alkanoyl groups having four carbon atoms may be straight chain or branched chain. Halo means fluoro, chloro, bromo or iodo.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as enantiomers or diastereoisomers. Furthermore, certain compounds of formula (I) which contain alkenyl groups may exist as cis-isomers or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with organo-carboxylic acids, or with organo-sulphonic acids. Compounds of formula (I) can also provide pharmaceutically acceptable metal salts, in particular non-toxic alkali metal salts, with bases. Examples include the sodium and potassium salts.

A preferred group of compounds of formula (I) is that wherein R¹ is H, methyl or ethyl; R² is C₁-C₃ alkyl; R³ is C₂-C₃ alkyl or allyl; R⁴ is C₁-C₂ alkyl optionally substituted with OH, NR⁵R⁶, CN, CONR⁵R⁶ or CO₂R⁷; acetyl optionally substituted with NR⁵R⁶; hydroxyethyl optionally substituted with NR⁵R⁶; ethoxymethyl optionally substituted with OH or NR⁵R⁶; CH=CHCN; CH=CHCONR⁵R⁶; CH=CHCO₂R⁷; CONR⁵R⁶; CO₂H; Br; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; SO₂NR⁹R¹⁰; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R⁵ and R⁶ are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-N(R¹¹)-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH; R⁷ is H or t-butyl; R⁸ is methyl or CH₂CH₂CH₂NR⁵R⁶; R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a piperidino or 4-N(R¹²)-piperazinyl group wherein said group is optionally substituted with NR¹³R¹⁴ or CONR¹³R¹⁴; R¹¹ is H, methyl, benzyl, 2-hydroxyethyl or acetyl; R¹² is H, C₁-C₃ alkyl, (hydroxy)C₂-C₃ alkyl, CSNR¹³R¹⁴ or C(NH)NR¹³R¹⁴; and R¹³ and R¹⁴ are each independently H or methyl.

A more preferred group of compounds of formula (I) is that wherein R¹ is methyl or ethyl; R² is C₁-C₃ alkyl; R³ is ethyl, n-propyl or allyl; R⁴ is CH₂NR⁵R⁶, COCH₂NR⁵R⁶, CH(OH)CH₂NR⁵R⁶, CH₂OCH₂CH₃, CH₂OCH₂CH₂OH, CH₂OCH₂CH₂NR⁵R⁶, CH=CHCON(CH₃)₂, CH=CHCO₂R⁷, CONR⁵R⁶, CO₂H, Br, NHSO₂NR⁵R⁶, NHSO₂CH₂CH₂CH₂NR⁵R⁶, SO₂NR⁹R¹⁰, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R⁵ and R⁶ together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-N(R¹¹)-piperazinyl or 2-methyl-1-imidazolyl group; R⁷ is H or t-butyl; R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a 4-carbamoylpiperidino or 4-N(R¹²)-piperazinyl group; R¹¹ is H, methyl, benzyl, 2-hydroxyethyl or acetyl; and R¹² is H, C₁-C₃ alkyl, 2-hydroxyethyl or CSNH₂.

A particularly preferred group of compounds of formula (I) is that wherein R¹ is methyl or ethyl; R² is n-propyl; R³ is ethyl, n-propyl or allyl; R⁴ is COCH₂NR⁵R⁶, CONR⁵R⁶, SO₂NR⁹R¹⁰ or 1-methyl-2-imidazolyl; R⁵ and R⁶ together with the nitrogen atom to which they are attached form a morpholino or 4-N(R¹¹)-piperazinyl group; R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a 4-N(R¹²)-piperazinyl group; R¹¹ is methyl or acetyl; and R¹² is H, methyl, 2-propyl or 2-hydroxyethyl.

Especially preferred individual compounds of the invention include:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimi-

din-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The compounds of formula (I) and their pharmaceutically acceptable salts, processes for the preparation thereof, *in vitro* test methods for determining the cGMP PDE and cAMP PDE inhibitory activities thereof, pharmaceutical compositions thereof and routes of administration for human use, are described in EP-A-0463756 and EP-A-0526004.

A preliminary investigation was carried out with a view to isolating and characterising the cyclic nucleotide PDEs of human corpus cavernosum, relaxation of which leads to penile erection. Studies of substrate specificity, response to activators and inhibitor sensitivity, have demonstrated that human corpus cavernosum contains three distinct PDE enzymes.

Methods

Fresh frozen human penis was obtained from IIAM (Pennsylvania). Tissue was thawed at room temperature, the corpus cavernosum was dissected from the penis to yield approximately 2-4 g of tissue and the following isolation protocol was followed. Tissue was coarsely chopped in ice-cold isotonic buffer (35 ml) containing 250mM sucrose, 1mM EDTA, 0.5mM PMSF and 20mM HEPES, pH 7.2, and the mixture subjected to brief (1 min.) treatment with a Silversen mixer/emulsifier. Homogenates were prepared using homogeniser tubes with teflon pestles and soluble fraction was prepared by centrifugation at 100,000 x g for 60 min. at 4°C. 10 ml of high speed supernatant was applied to a Pharmacia Mono Q anion exchange column (1 ml bed volume) equilibrated with buffer containing 1mM EDTA, 0.5 mM PMSF and 20mM HEPES, pH 7.2 (chromatography buffer). The column was then washed with 5 bed volumes of chromatography buffer, after which PDEs were eluted using a continuous gradient of 0-500mM NaCl (total volume 35 ml) and 1 ml fractions collected.

Column fractions were assayed for PDE activity using 500nM cGMP or 500nM cAMP as substrate. cAMP PDE activity was also determined in the presence of 1µM unlabelled cGMP and the PDE activity of selected fractions was determined in the presence of 10mM CaCl₂ and 10 units/ml bovine brain calmodulin. Appropriate fractions were pooled and stored at 4°C during the course of the study.

Inhibition studies were performed using a substrate concentration of 500nM throughout. All inhibitors were dissolved in DMSO and concentration-response curves were constructed over the range 3×10^{-10} to 1×10^{-4} M in half log increments. IC₅₀ values were calculated using the sigmoidal curve fitting algorithm of Biostat.

Results

Human corpus cavernosum soluble PDEs were separated into three distinct fractions of activity. The first, fraction I, (designated by order of elution) represents the major PDE present and is highly selective for cGMP as substrate. This fraction was found to be insensitive to stimulation by calcium/calmodulin and was classified as PDE_V. Fraction II hydrolyses cGMP and cAMP, with the latter activity being stimulated in the presence of cGMP, and is classified as PDE_{II}, whilst fraction III is cAMP selective and this activity is inhibited in the presence of cGMP, consistent with PDE_{III} activity.

In order to further characterise the PDE isoenzymes present in the tissue, studies were performed using a variety of inhibitors. Inhibitor studies with fractions I and II were performed using cGMP as substrate, whilst fraction III studies utilised cAMP. These studies confirmed that fraction I corresponds to PDE_V, whilst fraction III was clearly identified as PDE_{III}; fraction II (PDE_{II}) was relatively insensitive to all the inhibitors tested.

In summary, the above investigation identified three PDE isoenzymes in human corpus cavernosum tissue. The predominant PDE is the cGMP-specific PDE_V, whilst cGMP-stimulated cAMP PDE_{II} and cGMP-inhibited cAMP PDE_{III} are also present.

The compounds of the invention have been tested *in vitro* and found to be potent and selective inhibitors of the cGMP-specific PDE_V. For example, one of the especially preferred compounds of the invention has an IC₅₀ = 6.8 nM v.

the PDE_V enzyme, but demonstrates only weak inhibitory activity against the PDE_{II} and PDE_{III} enzymes with IC₅₀ = >100 μ M and 34 μ M respectively. Thus relaxation of the corpus cavernosum tissue and consequent penile erection is presumably mediated by elevation of cGMP levels in the said tissue, by virtue of the PDE inhibitory profile of the compounds of the invention.

Furthermore, none of the compounds of the invention tested in rat and dog, both intravenously (i.v.) and orally (p.o.) at up to 3 mg/Kg, has shown any overt sign of adverse acute toxicity. In mouse, no deaths occurred after doses of up to 100 mg/Kg i.v.. Certain especially preferred compounds showed no toxic effects on chronic p.o. administration to rat at up to 10 mg/Kg and to dog at up to 20 mg/Kg.

In man, certain especially preferred compounds have been tested orally in both single dose and multiple dose volunteer studies. Moreover, patient studies conducted thus far have confirmed that one of the especially preferred compounds induces penile erection in impotent males.

Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.

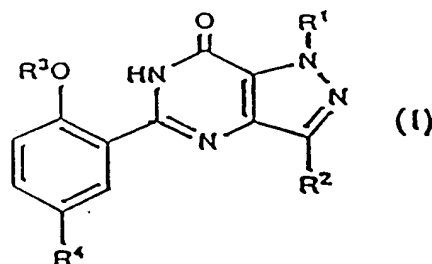
Generally, in man, oral administration of the compounds of the invention is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. A preferred dosing regimen for a typical man is 5 to 75 mg of compound three times daily. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

For veterinary use, a compound of formula (I) or a non-toxic salt thereof is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular male animal.

Moreover, the invention includes the use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic oral treatment of erectile dysfunction in man.

Claims

1. The use of a compound of formula (I):



wherein

R¹ is H; C₁-C₃ alkyl; C₁-C₃ perfluoroalkyl; or C₃-C₅ cycloalkyl;

R² is H; C₁-C₆ alkyl optionally substituted with C₃-C₆ cycloalkyl; C₁-C₃ perfluoroalkyl; or C₃-C₆ cycloalkyl;

R³ is C₁-C₆ alkyl optionally substituted with C₃-C₆ cycloalkyl; C₁-C₆ perfluoroalkyl; C₃-C₅ cycloalkyl; C₃-C₆ alkenyl; or C₃-C₆ alkynyl;

R⁴ is C₁-C₄ alkyl optionally substituted with OH, NR⁵R⁶, CN, CONR⁵R⁶ or CO₂R⁷; C₂-C₄ alkenyl optionally substituted with CN, CONR⁵R⁶ or CO₂R⁷; C₂-C₄ alkanoyl optionally substituted with NR⁵R⁶; (hydroxy)C₂-C₄ alkyl optionally substituted with NR⁵R⁶; (C₂-C₃ alkoxy)C₁-C₂ alkyl optionally substituted with OH or NR⁵R⁶; CONR⁵R⁶; CO₂R⁷; halo; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; SO₂NR⁹R¹⁰; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;

R⁵ and R⁶ are each independently H or C₁-C₄ alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-N(R¹¹)-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;

R⁷ is H or C₁-C₄ alkyl;

R⁸ is C₁-C₃ alkyl optionally substituted with NR⁵R⁶;

R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, mor-

pholino or 4-N(R¹²)-piperazinyl group wherein said group is optionally substituted with C₁-C₄ alkyl, C₁-C₃ alkoxy, NR¹³R¹⁴ or CONR¹³R¹⁴;

R¹¹ is H; C₁-C₃ alkyl optionally substituted with phenyl; (hydroxy)C₂-C₃ alkyl; or C₁-C₄ alkanoyl;

R¹² is H; C₁-C₆ alkyl; (C₁-C₃ alkoxy)C₂-C₆ alkyl; (hydroxy)C₂-C₆ alkyl; (R¹³R¹⁴N)C₂-C₆ alkyl; (R¹³R¹⁴NOC)C₁-C₆ alkyl; CONR¹³R¹⁴; CSNR¹³R¹⁴; or C(NH)NR¹³R¹⁴;

and

R¹³ and R¹⁴ are each independently H; C₁-C₄ alkyl; (C₁-C₃ alkoxy)C₂-C₄ alkyl; or (hydroxy)C₂-C₄ alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

2. The use according to claim 1 wherein in the compound of formula (I) R¹ is H, methyl or ethyl; R² is C₁-C₃ alkyl; R³ is C₂-C₃ alkyl or allyl; R⁴ is C₁-C₂ alkyl optionally substituted with OH, NR⁵R⁶, CN, CONR⁵R⁶ or CO₂R⁷; acetyl optionally substituted with NR⁵R⁶; hydroxyethyl optionally substituted with NR⁵R⁶; ethoxymethyl optionally substituted with OH or NR⁵R⁶; CH=CHCN; CH=CHCONR⁵R⁶; CH=CHCO₂R⁷; CONR⁵R⁶; CO₂H; Br; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; SO₂NR⁹R¹⁰; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R⁵ and R⁶ are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-N(R¹¹)-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH; R⁷ is H or t-butyl; R⁸ is methyl or CH₂CH₂CH₂NR⁵R⁶; R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a piperidino or 4-N(R¹²)-piperazinyl group wherein said group is optionally substituted with NR¹³R¹⁴ or CONR¹³R¹⁴; R¹¹ is H, methyl, benzyl, 2-hydroxyethyl or acetyl; R¹² is H, C₁-C₃ alkyl, (hydroxy)C₂-C₃ alkyl, CSNR¹³R¹⁴ or C(NH)NR¹³R¹⁴; and R¹³ and R¹⁴ are each independently H or methyl.
3. The use according to claim 2 wherein in the compound of formula (I) R¹ is methyl or ethyl; R² is C₁-C₃ alkyl; R³ is ethyl, n-propyl or allyl; R⁴ is CH₂NR⁵R⁶, COCH₂NR⁵R⁶, CH(OH)CH₂NR⁵R⁶, CH₂OCH₂CH₃, CH₂OCH₂CH₂OH, CH₂OCH₂CH₂NR⁵R⁶, CH=CHCON(CH₃)₂, CH=CHCO₂R⁷, CONR⁵R⁶, CO₂H, Br, NHSO₂NR⁵R⁶, NHSO₂CH₂CH₂CH₂NR⁵R⁶, SO₂NR⁹R¹⁰, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R⁵ and R⁶ together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-N(R¹¹)-piperazinyl or 2-methyl-1-imidazolyl group; R⁷ is H or t-butyl; R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a 4-carbamoylpiperidino or 4-N(R¹²)-piperazinyl group; R¹¹ is H, methyl, benzyl, 2-hydroxyethyl or acetyl; and R¹² is H, C₁-C₃ alkyl, 2-hydroxyethyl or CSNH₂.
4. The use according to claim 3 wherein in the compound of formula (I) R¹ is methyl or ethyl; R² is n-propyl; R³ is ethyl, n-propyl or allyl; R⁴ is COCH₂NR⁵R⁶, CONR⁵R⁶, SO₂NR⁹R¹⁰ or 1-methyl-2-imidazolyl; R⁵ and R⁶ together with the nitrogen atom to which they are attached form a morpholino or 4-N(R¹¹)-piperazinyl group; R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a 4-N(R¹²)-piperazinyl group; R¹¹ is methyl or acetyl; and R¹² is H, methyl, 2-propyl or 2-hydroxyethyl.
5. The use according to claim 4 wherein the compound of formula (I) is selected from:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

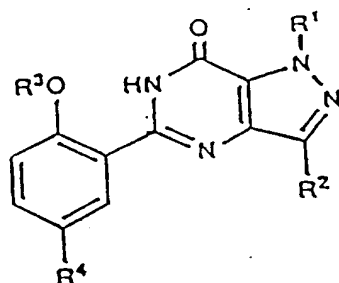
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

6. The use according to claim 5 wherein the compound of formula (I) is 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.
7. The use according to claim 5 wherein the compound of formula (I) is 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.
8. The use of a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of female sexual dysfunction.
9. The use according to any one of claims 1 to 8 wherein the medicament is adapted for oral treatment.
10. The use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic oral treatment of erectile dysfunction in man.
11. The use according to claim 10 wherein the inhibitor is a cGMP PDE_V inhibitor.

Patentansprüche

1. Verwendung einer Verbindung der Formel (I):



(I) ,

worin

R¹ bedeutet: H; C₁-C₃-Alkyl; C₁-C₃-Perfluoralkyl; oder C₃-C₅-Cycloalkyl;

R² darstellt: H; C₁-C₆-Alkyl, gegebenenfalls substituiert mit C₃-C₆-Cycloalkyl; C₁-C₃-Perfluoralkyl; oder C₃-C₆-Cycloalkyl;

R³ ist: C₁-C₆-Alkyl, gegebenenfalls substituiert mit C₃-C₆-Cycloalkyl; C₁-C₆-Perfluoralkyl; C₃-C₅-Cycloalkyl; C₃-C₆-Alkenyl; oder C₃-C₆-Alkyl;

R⁴ bedeutet: C₁-C₄-Alkyl, gegebenenfalls substituiert mit OH, NR⁵R⁶, CN, CONR⁵R⁶ oder CO₂R⁷; C₂-C₄-Alkenyl, gegebenenfalls substituiert mit CN, CONR⁵R⁶ oder CO₂R⁷; C₂-C₄-Alkanoyl, gegebenenfalls substituiert mit NR⁵R⁶; (Hydroxy)-C₂-C₄-alkyl, gegebenenfalls substituiert mit NR⁵R⁶; (C₂-C₃-Alkoxy)-C₁-C₂-alkyl, gegebenenfalls substituiert mit OH oder NR⁵R⁶; CONR⁵R⁶; CO₂R⁷; Halogen; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; SO₂NR⁹R¹⁰; oder Phenyl, Pyridyl, Pyrimidinyl, Imidazolyl, Oxazolyl, Thiazolyl, Thienyl oder Triazolyl, von denen jedes gegebenenfalls substituiert ist mit Methyl;

R⁵ und R⁶ jeweils unabhängig H oder C₁-C₄-Alkyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Pyrrolidinyl-, Piperidino-, Morpholino-, 4-N(R¹¹)-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder OH;

R⁷ H oder C₁-C₄-Alkyl ist;

R⁸ C₁-C₃-Alkyl, gegebenenfalls substituiert mit NR⁵R⁶, bedeutet;

R⁹ und R¹⁰ zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Pyrrolidinyl-, Piperidino-, Morpholino-, 4-N(R¹²)-Piperazinyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit C₁-C₄-Alkyl, C₁-C₃-Alkoxy, NR¹³R¹⁴ oder CONR¹³R¹⁴;

R¹¹ darstellt: H; C₁-C₃-Alkyl, gegebenenfalls substituiert mit Phenyl; (Hydroxy)-C₂-C₃-alkyl; oder C₁-C₄-Alkanoyl;

R¹² ist: H; C₁-C₆-Alkyl; (C₁-C₃-Alkoxy)-C₂-C₆-alkyl; (Hydroxy)-C₂-C₆-alkyl; (R¹³R¹⁴N)-C₂-C₆-Alkyl;

($R^{13}R^{14}NOC$)- C_1 - C_6 -Alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; oder $C(NH)NR^{13}R^{14}$; und R^{13} und R^{14} jeweils unabhängig H; C_1 - C_4 -Alkyl; (C_1 - C_3 -Alkoxy)- C_2 - C_4 -alkyl; oder (Hydroxy)- C_2 - C_4 -alkyl bedeuten;

oder eines pharmazeutisch annehmbaren Salzes hiervon, oder einer pharmazeutischen Zusammensetzung, die eine der Einheiten enthält, bei der Herstellung eines Medikaments zur kurativen oder prophylaktischen Behandlung von erektiler Dysfunktion bei einem männlichen Tier, einschließlich Männern.

2. Verwendung nach Anspruch 1, wobei in der Verbindung der Formel (I)

R^1 H, Methyl oder Ethyl bedeutet;
 R^2 C_1 - C_3 -Alkyl darstellt;
 R^3 C_2 - C_3 -Alkyl oder Allyl ist;
 R^4 bedeutet: C_1 - C_2 -Alkyl, gegebenenfalls substituiert mit OH, NR^5R^6 , CN, $CONR^5R^6$ oder CO_2R^7 ; Acetyl, gegebenenfalls substituiert mit NR^5R^6 ; Hydroxyethyl, gegebenenfalls substituiert mit NR^5R^6 ; Ethoxymethyl, gegebenenfalls substituiert mit OH oder NR^5R^6 ; $CH=CHCN$; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; $CONR^5R^6$; CO_2H ; Br; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; oder Pyridyl oder Imidazolyl, von denen jedes gegebenenfalls substituiert ist mit Methyl;
 R^5 und R^6 jeweils unabhängig H, Methyl oder Ethyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, Morpholino-, 4-N(R^{11})-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder OH;
 R^7 H oder tert. Butyl ist;
 R^8 Methyl oder $CH_2CH_2CH_2NR^5R^6$ bedeutet;
 R^9 und R^{10} zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino- oder 4-N(R^{12})-Piperazinyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit $NR^{13}R^{14}$ oder $CONR^{13}R^{14}$;
 R^{11} H; Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl darstellt;
 R^{12} H; C_1 - C_3 -Alkyl, (Hydroxy)- C_2 - C_3 -alkyl, $CSNR^{13}R^{14}$ oder $C(NH)NR^{13}R^{14}$ ist; und
 R^{13} und R^{14} jeweils unabhängig H oder Methyl bedeuten.

3. Verwendung nach Anspruch 2, wobei in der Verbindung der Formel (I)

R^1 Methyl oder Ethyl bedeutet;
 R^2 C_1 - C_3 -Alkyl darstellt;
 R^3 Ethyl, n-Propyl oder Allyl ist;
 R^4 $CH_2NR^5R^6$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $CH_2OCH_2CH_2NR^5R^6$, $CH=CHCON(CH_3)_2$, $CH=CHCO_2R^7$, $CONR^5R^6$, CO_2H , Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, $SO_2NR^9R^{10}$, 2-Pyridyl, 1-Imidazolyl oder 1-Methyl-2-imidazolyl bedeutet;
 R^5 und R^6 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, 4-Hydroxypiperidino-, Morpholino-, 4-N(R^{11})-Piperazinyl- oder 2-Methyl-1-imidazolyl-Gruppe bilden;
 R^7 H oder tert. Butyl ist;
 R^9 und R^{10} zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine 4-Carbamoylpiperidino- oder 4-N(R^{12})-Piperazinyl-Gruppe bilden;
 R^{11} H, Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl darstellt; und
 R^{12} H, C_1 - C_3 -Alkyl, 2-Hydroxyethyl oder $CSNH_2$ ist.

4. Verwendung nach Anspruch 3, wobei in der Verbindung der Formel (I)

R^1 Methyl oder Ethyl bedeutet;
 R^2 n-Propyl darstellt;
 R^3 Ethyl, n-Propyl oder Allyl ist;
 R^4 $COCH_2NR^5R^6$, $CONR^5R^6$, $SO_2NR^9R^{10}$ oder 1-Methyl-2-imidazolyl bedeutet;
 R^5 und R^6 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Morpholino- oder 4-N(R^{11})-Piperazinyl-Gruppe bilden;
 R^9 und R^{10} zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine 4-N(R^{12})-Piperazinyl-Gruppe bilden;
 R^{11} Methyl oder Acetyl darstellt; und
 R^{12} H, Methyl, 2-Propyl oder 2-Hydroxyethyl ist.

5. Verwendung nach Anspruch 4, wobei die Verbindung der Formel (I) ausgewählt wird aus:

5-(2-Ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
 5-(5-Morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
 5-[2-Ethoxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-
 d]pyrimidin-7-on;
 5-[2-Allyloxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-
 d]pyrimidin-7-on;
 5-[2-Ethoxy-5-[4-(2-propyl)-1-piperazinylsulfonyl]-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-
 d]pyrimidin-7-on;
 5-[2-Ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulfonyl]-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyra-
 zolo[4,3-d]pyrimidin-7-on;
 5-[5-[4-(2-Hydroxyethyl)-1-piperazinylsulfonyl]-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyra-
 zolo[4,3-d]pyrimidin-7-on;
 5-[2-Ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-
 d]pyrimidin-7-on; und
 5-[2-Ethoxy-5-(1-methyl-2-imidazolyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-
 on.

6. Verwendung nach Anspruch 5, wobei die Verbindung der Formel (I) 5-[2-Ethoxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on ist.

7. Verwendung nach Anspruch 5, wobei die Verbindung der Formel (I) 5-(2-Ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on ist.

8. Verwendung einer Verbindung der Formel (I), wie in einem der Ansprüche 1 bis 7 definiert, oder eines pharmazeutisch annehmbaren Salzes hievon, oder einer pharmazeutischen Zusammensetzung, die eine der Einheiten enthält, bei der Herstellung eines Medikaments zur kurativen oder prophylaktischen Behandlung weiblicher sexueller Dysfunktion.

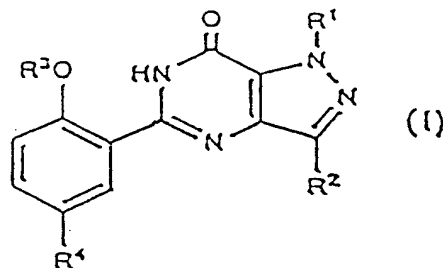
9. Verwendung nach einem der Ansprüche 1 bis 8, wobei das Medikament für eine orale Behandlung geeignet ist.

10. Verwendung eines cGMP PDE-Inhibitors, oder eines pharmazeutisch annehmbaren Salzes hievon, oder einer pharmazeutischen Zusammensetzung, die eine der Einheiten enthält, bei der Herstellung eines Medikaments zur kurativen oder prophylaktischen oralen Behandlung von erektiler Dysfunktion bei Männern.

11. Verwendung nach Anspruch 10, wobei der Inhibitor ein cGMP PDE_V-Inhibitor ist.

Revendications

1. Utilisation d'un composé de formule (I) :



dans laquelle :

R¹ représente H ; alkyle en C₁-C₃ ; perfluoroalkyle en C₁-C₃ ; ou cycloalkyle en C₃-C₅ ;
 R² représente H ; alkyle en C₁-C₆ facultativement substitué par cycloalkyle en C₃-C₆ ; perfluoroalkyle en C₁-C₃ ; ou cycloalkyle en C₃-C₆ ;

R³ représente alkyle en C₁-C₆ facultativement substitué par cycloalkyle en C₃-C₆ ; perfluoroalkyle en C₁-C₆ ; cycloalkyle en C₃-C₅ ; alkényle en C₃-C₆ ; ou alkynyle en C₃-C₆ ;

R⁴ représente alkyle en C₁-C₄ facultativement substitué par OH, NR⁵R⁶, CN, CONR⁵R⁶ ou CO₂R⁷ ; alkényle en C₂-C₄ facultativement substitué par CN, CONR⁵R⁶ ou CO₂R⁷ ; alcanoyloxy en C₂-C₄ facultativement substitué par NR⁵R⁶ ; (hydroxy)alkyle en C₂-C₄ facultativement substitué par NR⁵R⁶ ; (alcoyloxy en C₂-C₃)alkyle en C₁-C₂ facultativement substitué par OH ou NR⁵R⁶ ; CONR⁵R⁶ ; CO₂R⁷ ; halogéno ; NR⁵R⁶ ; NHSO₂NR⁵R⁶ ; NHSO₂R⁸ ; SO₂NR⁹R¹⁰ ; ou phényle, pyridyle, pyrimidinyle, imidazolyle, oxazolyle, thiazolyle, thiényloxy ou triazolyle dont l'un quelconque est facultativement substitué par méthyle ;

R⁵ et R⁶ représentent chacun indépendamment H ou alkyle en C₁-C₄, ou représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe pyrrolidinyle, pipéridino, morpholino, 4-N(R¹¹)-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou OH ;

R⁷ représente H ou alkyle en C₁-C₄ ;

R⁸ représente alkyle en C₁-C₃ facultativement substitué par NR⁵R⁶ ;

R⁹ et R¹⁰ représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe pyrrolidinyle, pipéridino, morpholino ou 4-N(R¹²)-pipérazinyle, ledit groupe étant facultativement substitué par alkyle en C₁-C₄, alcoyloxy en C₁-C₃, NR¹³R¹⁴ ou CONR¹³R¹⁴ ;

R¹¹ représente H ; alkyle en C₁-C₃ facultativement substitué par phényle ; (hydroxy)alkyle en C₂-C₃ ; ou alcanoyloxy en C₁-C₄ ;

R¹² représente H ; alkyle en C₁-C₆ ; (alcoyloxy en C₁-C₃)alkyle en C₂-C₆ ; (hydroxy)alkyle en C₂-C₆ ; (R¹³R¹⁴N)alkyle en C₂-C₆ ; (R¹³R¹⁴NO)alkyle en C₁-C₆ ; CONR¹³R¹⁴ ; CSNR¹³R¹⁴ ; ou C(NH)NR¹³R¹⁴ ; et R¹³ et R¹⁴ représentent chacun indépendamment H, alkyle en C₁-C₄ ; (alcoyloxy en C₁-C₃)alkyle en C₂-C₄ ; ou (hydroxy)alkyle en C₂-C₄ ;

ou un sel pharmaceutiquement acceptable, ou une composition pharmaceutique contenant ledit composé ou ledit sel, pour la fabrication d'un médicament en vue du traitement curatif ou prophylactique d'un dysfonctionnement érectile chez un animal mâle, y compris l'homme.

2. Utilisation selon la revendication 1, dans laquelle, dans le composé de formule (I), R¹ représente H, méthyle ou éthyle ; R² représente alkyle en C₁-C₃ ; R³ représente alkyle en C₂-C₃ ou allyle ; R⁴ représente alkyle en C₁-C₂ facultativement substitué par OH, NR⁵R⁶, CN, CONR⁵R⁶ ou CO₂R⁷ ; acétyloxy facultativement substitué par NR⁵R⁶ ; hydroxyéthyle facultativement substitué par NR⁵R⁶ ; éthoxyméthyle facultativement substitué par OH ou NR⁵R⁶ ; CH=CHCN ; CH=CHCONR⁵R⁶ ; CH=CHCO₂R⁷ ; CONR⁵R⁶ ; CO₂H ; Br ; NR⁵R⁶ ; NHSO₂NR⁵R⁶ ; NHSO₂R⁸ ; SO₂NR⁹R¹⁰ ; ou pyridyle ou imidazolyle dont l'un quelconque est facultativement substitué par méthyle ; R⁵ et R⁶ représentent chacun indépendamment H, méthyle ou éthyle, ou représentent ensemble, avec l'atome d'azote auquel ils sont liés un groupe pipéridino, morpholino, 4-N(R¹¹)-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou OH ; R⁷ représente H ou t-butyle ; R⁸ représente méthyle ou CH₂CH₂CH₂NR⁵R⁶ ; R⁹ et R¹⁰ représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe pipéridino ou 4-N(R¹²)-pipérazinyle, ledit groupe étant facultativement substitué par NR¹³R¹⁴ ou CONR¹³R¹⁴ ; R¹¹ représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyloxy ; R¹² représente H, alkyle en C₁-C₃, (hydroxy)alkyle en C₂-C₃, CSNR¹³R¹⁴ ou C(NH)NR¹³R¹⁴ ; et R¹³ et R¹⁴ représentent chacun indépendamment H ou méthyle.

3. Utilisation selon la revendication 2, dans laquelle, dans le composé de formule (I), R¹ représente méthyle ou éthyle ; R² représente alkyle en C₁-C₃ ; R³ représente éthyle, n-propyle ou allyle ; R⁴ représente CH₂NR⁵R⁶, COCH₂NR⁵R⁶, CH(OH)CH₂NR⁵R⁶, CH₂OCH₂CH₃, CH₂OCH₂CH₂OH, CH₂OCH₂CH₂CH₂NR⁵R⁶, CH=CHCON(CH₃)₂, CH=CHCO₂R⁷, CONR⁵R⁶, CO₂H, Br, NHSO₂NR⁵R⁶, NHSO₂CH₂CH₂CH₂CH₂NR⁵R⁶, SO₂NR⁹R¹⁰, 2-pyridyle, 1-imidazolyle ou 1-méthyl-2-imidazolyle ; R⁵ et R⁶ représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe pipéridino, 4-hydroxypipéridino, morpholino, 4-N(R¹¹)-pipérazinyle ou 2-méthyl-1-imidazolyle ; R⁷ représente H ou t-butyle ; R⁹ et R¹⁰ représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe 4-carbamoylpipéridino ou 4-N(R¹²)-pipérazinyle ; R¹¹ représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyloxy et R¹² représente H, alkyle en C₁-C₃, 2-hydroxyéthyle ou CSNH₂.

4. Utilisation selon la revendication 3, dans laquelle, dans le composé de formule (I), R¹ représente méthyle ou éthyle ; R² représente n-propyle ; R³ représente éthyle, n-propyle ou allyle ; R⁴ représente COCH₂NR⁵R⁶, CONR⁵R⁶, SO₂NR⁹R¹⁰ ou 1-méthyl-2-imidazolyle ; R⁵ et R⁶ représentent ensemble, avec l'atome d'azote auquel ils sont liés un groupe morpholino ou 4-N(R¹¹)-pipérazinyle ; R⁹ et R¹⁰ représentent ensemble, avec l'atome d'azote auquel ils sont liés, un groupe 4-N(R¹²)-pipérazinyle ; R¹¹ représente méthyle ou acétyloxy ; et R¹² représente H, méthyle, 2-propyle ou 2-hydroxyéthyle.

5. Utilisation selon la revendication 4, dans laquelle le composé de formule (I) est choisi parmi :

la 5-(2-éthoxy-5-morpholinoacétylphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
 la 5-(5-morpholinoacétyl-2-n-propoxyphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
 la 5-[2-éthoxy-5-(4-méthyl-1-pipérazinylsulphonyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
 la 5-[2-allyloxy-5-(4-méthyl-1-pipérazinylsulphonyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
 la 5-{2-éthoxy-5-[4-(2-propyl)-1-pipérazinylsulphonyl]phényl}-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
 la 5-{2-éthoxy-5-[4-(2-hydroxyéthyl)-1-pipérazinylsulphonyl]phényl}-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
 la 5-[5-[4-(2-hydroxyéthyl)-1-pipérazinylsulphonyl]-2-n-propoxyphényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
 la 5-[2-éthoxy-5-(4-méthyl-1-pipérazinylcarbonyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ; et
 la 5-[2-éthoxy-5-(1-méthyl-2-imidazolyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

6. Utilisation selon la revendication 5, dans laquelle le composé de formule (I) est la 5-[2-éthoxy-5-(4-méthyl-1-pipérazinylsulfonyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

7. Utilisation selon la revendication 5, dans laquelle le composé de formule (I) est la 5-(2-éthoxy-5-morpholinoacétylphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

8. Utilisation d'un composé de formule (I) tel que défini dans l'une quelconque des revendications 1 à 7, ou d'un sel pharmaceutiquement acceptable d'un tel composé, ou d'une composition pharmaceutique contenant ledit composé ou ledit sel pour la fabrication d'un médicament pour le traitement curatif ou prophylactique d'un dysfonctionnement sexuel féminin.

9. Utilisation selon l'une quelconque des revendications 1 à 8, dans laquelle le médicament est adapté à un traitement par voie orale.

10. Utilisation d'un inhibiteur de la cGMP PDE, ou d'un sel pharmaceutiquement acceptable d'un tel composé, ou d'une composition pharmaceutique contenant ledit composé ou ledit sel, pour la fabrication d'un médicament pour le traitement curatif ou prophylactique par voie orale d'un dysfonctionnement érectile chez l'homme.

11. Utilisation selon la revendication 10, dans laquelle l'inhibiteur est un inhibiteur de la cGMP PDE_v.